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Effect of Direct Fetal Opioid Analgesia on Fetal Hormonal and Hemodynamic Stress Response to Intrauterine Needling

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Background: **Whether the fetus can experience pain remains controversial. During the last half of pregnancy, the neuroanatomic connections for nociception are in place, and the human fetus mounts sizable stress responses to physical insults. Analgesia has been recommended for intrauterine procedures or late termination, but without evidence that it works. The authors investigated whether fentanyl ablates the fetal stress response to needling using the model of delayed interval sampling during intrahepatic vein blood sampling and transfusion in alloimmunized fetuses undergoing intravascular transfusion between 20 and 35 weeks.**

Methods: **Intravenous fentanyl (10 μg/kg estimated fetal weight × 1.25 placental correction) was given once at intrahepatic vein transfusion in 16 fetuses, and changes (posttransfusion − pretransfusion) in β endorphin, cortisol, and middle cerebral artery pulsatility index were compared with intrahepatic vein transfusions without fentanyl and with control transfusions at the placental cord insertion.**

Results: **Fentanyl reduced the β endorphin (mean difference in changes, −70.3 pg/ml; 95% confidence interval, −121 to −19.2; $P = 0.02$) and middle cerebral artery pulsatility index response (mean difference, 0.65; 95% confidence interval, 0.26–1.04; $P = 0.03$), but not the cortisol response (mean difference, −10.9 ng/ml, 95% confidence interval, −24.7 to 2.9; $P = 0.11$) in fetuses who had paired intrahepatic vein transfusions with and without fentanyl. Comparison with control fetuses transfused without fentanyl indicated that the β endorphin and cerebral Doppler response to intrahepatic vein transfusion with fentanyl approached that of nonstressful placental cord transfusions.**

Conclusions: **The authors conclude that intravenous fentanyl attenuates the fetal stress response to intrahepatic vein needling.**

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IT is now generally accepted that newborn babies are capable of experiencing pain, and provision of analgesia for neonatal medical and surgical procedures has become standard of care.[1] Opioid analgesia for minor and major procedures has been shown in randomized trials to reduce metabolic and biophysical stress responses, postoperative morbidity and mortality, and abnormal imprinting of subsequent pain responses in infancy.[2–4]

Applying the subjective concept of pain to a fetus is problematic.[5–7] Nevertheless, if a preterm baby is deemed capable of painful experience and to warrant analgesia, there seems no physiological reason why a fetus of the same gestational age should not be treated similarly. The full anatomic pathways necessary for nociception are in place by 24–28 weeks, when the thalamocortical fibers penetrate the cortical plate.[5,7,8] Earlier nociceptive experience may be possible from around midgestation, mediated *via* transient thalamocortical fibers.[5] Indeed, the descending inhibitory pathways do not form until after birth, raising the possibility that the fetus may be more sensitive to noxious stimuli than the older child.

Our group has shown that the human fetus from 18–20 weeks elaborates pituitary-adrenal, sympatho-adrenal, and circulatory stress responses to physical insults.[9–13] These have been characterized using clinically indicated intrauterine transfusion by ultrasound-guided needling as an ethically acceptable model of delayed serial blood sampling, comparing responses in procedures performed at the intrahepatic vein (IHV), which involves transgressing the fetal abdomen, with control procedures at the placental cord insertion (PCI), which is not innervated. After IHV procedures, fetal plasma cortisol and β endorphin increased twofold to sixfold, whereas the fetal middle cerebral artery (MCA) pulsatility index (PI) decreased by two SDs, consistent with the centralization or "brain sparing" response (in which blood flow is preferentially redistributed to the brain and other vital organs at the expense of the carcass).[10,12]

A number of authorities have advocated giving analgesia to fetuses,[8,14,15] although there is currently no evidence that analgesia blunts fetal nociceptive responses.

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Analgesia is relevant in late gestation to diagnostic and therapeutic invasive procedures, closed or open fetal surgery, and arguably late termination. The rationale is, first, the humanitarian one, when it is possible that the fetus experiences pain. Next are inferences from neonatal studies of short- and long-term benefits of analgesia.[2–4,16] In addition, animal studies indicate that a stressful perinatal event can have long-term effects on hippocampal development and stress behavior.[17–20] Although there is no evidence to date in humans that intrauterine insults imprint on subsequent stress behavior, stress responses to vaccination in infancy are known to be impaired in babies circumcised neonatally or born by difficult vaginal delivery.[2,21]

The synthetic μ-opioid receptor agonist, fentanyl, is widely used in neonatal anesthesia. Opioid receptors are abundant in the fetal spinal cord and brain stem by 20 weeks.[22,23] We tested the hypothesis that direct intravenous fentanyl administration reduces fetal hormonal and hemodynamic stress responses to IHV needling.

Material and Methods

Patients

We recruited women with singleton pregnancies undergoing clinically indicated serial intrauterine transfusions between 20 and 35 weeks for alloimmune fetal anemia or thrombocytopenia in two tertiary referral fetal medicine centers (London and Glasgow) between November 1996 and July 1999. Gestational age was based on certain menstrual dates or ultrasound 18 weeks or less. Fetal growth and well-being were assessed by ultrasound. Inclusion criteria were size appropriate for gestational age (abdominal circumference $\geq$ fifth centile), absence of structural anomalies, no evidence of hydrops, and positive end-diastolic frequencies in the umbilical artery Doppler waveform. Fetuses with hypoxemia (oxygen partial pressure < -2 z scores), aneuploidy, or severe anemia (hemoglobin $<$ 5 g/dl) were excluded, as were procedures that were difficult (time to access $>$ 10 min) or complicated by significant intraprocedural bradycardia (fetal heart rate $<$ 80 beats/min lasting $>$ 30s). All women gave written informed consent to administration of fentanyl as approved by our respective institutional Research Ethics Committees (Hammersmith Hospitals Trust, London, United Kingdom, and Yorkhill, Glasgow, United Kingdom). Because of the unknown effects on the developing brain, institutional ethical approval stipulated that the use of fentanyl be limited to a single occasion. The use of intravenous fentanyl in fetuses for research purposes was granted a Doctors' Exemption Certificate by the UK Medicines Control Agency, London, United Kingdom.

Intrauterine Transfusion

Local anesthetic (5–10 ml of 1% lidocaine) was infiltrated into the maternal abdomen, and a 20-gauge needle was guided into the fetal umbilical vein under ultrasound control. Neither maternal premedication nor fetal neuromuscular blockade was used. The site of fetal blood sampling, either the IHV or the PCI, was chosen by the operator based on technical factors and ease of approach. After confirming the purity of fetal samples, full blood count (Coulter Counter, Coulter Electronics Ltd., Luton, United Kingdom), blood gas analysis (Radiometer ABL 330, Copenhagen, Denmark), and karyotype was performed. Fresh warmed filtered antigen-negative erythrocyte or platelet concentrates cross-matched against the mother were administered intravascularly at 5–10 ml/min to achieve a fetal hemoglobin concentration of 13–17 g/dl or a platelet count of 500–700 $\times$ 10^9/l. The time to access the fetal circulation (fetal skin–cord to blood sample) and the duration of transfusion (from the pretransfusion sample) were recorded in seconds.

Fentanyl Procedures

After collection of clinical samples, an additional aliquot of fetal blood (0.5–1.5 ml) was withdrawn for hormone and fentanyl assay. Next, and before commencing transfusion, a bolus dose of fentanyl was administered intravenously to the fetus. The dose was calculated based on ultrasonically estimated fetal weight increased by 25% to account for the placental blood pool and given at a concentration of 10 μg/ml. After first trying 3 μg/kg fentanyl in pilot experiments, as recommended for children breathing spontaneously, we administered 10 μg/kg in the study, which is at the lower end of the range used in ventilated children and which has been shown to attenuate surgical stress responses in preterm neonates.[3] On completing the transfusion, a further aliquot of fetal blood was collected.

Fetal Doppler waveforms were obtained, as described previously,[12] before and immediately after transfusion in patients studied in London, where the Doppler Research Fellow was based. Briefly, the MCA was identified on color Doppler (Acuson XP10 or Sequoia, Mountain View, CA) at an angle of 35° or less in the near field of the biparietal diameter view. Waveforms were obtained by a single operator (J. T.) during fetal apnea on Super VHS videotape for subsequent analysis.

Control Procedures

We used a two-model design to compare fentanyl transfusions with two separate contemporaneous cohorts of nonfentanyl transfusions (fig. 1). First, paired longitudinal controls comprised the study pregnancies undergoing an additional IHV transfusion without fentanyl (n = 12, as 4 lacked comparable data from an IHV transfusion without fentanyl). The control transfusion

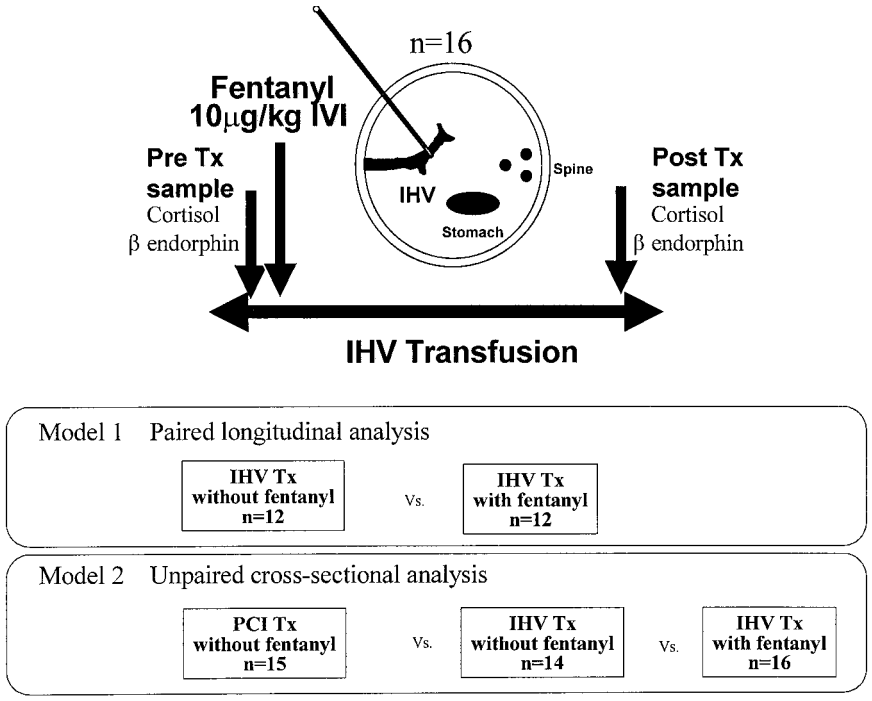

Fig. 1. The change in stress responses to intrahepatic vein (IHV) transfusion (Tx) after 10 μg/kg fentanyl was compared in a two-model design with a paired longitudinal control group of the same fetuses undergoing IHV transfusion without fentanyl, and unpaired cross-sectional control groups of different fetuses undergoing placental cord insertion (PCI) transfusion and IHV transfusions without fentanyl.

was usually the one immediately before (n = 5) or after the fentanyl one (n = 7), and their gestations differed by 2–4 weeks. Gestational age differences of this magnitude have not influenced the degree of response in our previous studies.[10,12,13] Because the fentanyl patients (n = 16) underwent insufficient contemporaneous control PCI transfusions, a further group of unpaired cross-sectional controls was studied (n = 15 PCI, 14 IHV) This comprised pregnant women undergoing intravascular transfusion who did not consent to fentanyl, did not undergo serial procedures, or did not have an IHV transfusion. The inclusion–exclusion criteria and study methods were as above, except that fentanyl was not administered. Baseline data for comparison are shown in tables 1 and 2. All women consented to additional blood collection and Doppler studies, as approved by our ethics committees.

Assays

Samples were stored at −80°C until batch assay by one of two investigators (R. G., X. G.) who were blind to the type of transfusion. Plasma cortisol and fentanyl were measured by solid-phase immunoassay (Diagnostic Products Corporation, Los Angeles, CA), with lower limits of sensitivity of 2 and 0.04 ng/ml, respectively. β endorphin was assayed in fetal venous plasma by two-site solid-phase immunoradiometric assay (Nichols Institute Diagnostics, San Juan, CA). Cross-reactivity with β lipotropin was 14%, and the lower limit of sensitivity was 14 pg/ml. Coefficients of variation in fetal blood were less than 6, 3, and 13% for cortisol, fentanyl, and β endorphin, respectively.

Doppler Analysis

The videotapes were reviewed using on-screen calipers, and the mean PI was calculated by the manufacturer's software from five consecutive waveforms. To exclude any effect of heart rate on PI, the instantaneous (not the baseline) heart rate was measured over the same

Table 1. Baseline Data for Paired Comparison of Fetuses Undergoing Two IHV Transfusions, One with 10 μg/kg Fentanyl and One Without

(n = 12)	Control Transfusion	Fentanyl Transfusion	Significance
Gestational age (weeks)	29.5 ± 4.5	29.2 ± 2.9	NS
Fetal hemoglobin (g/dl)	10.0 ± 2.3	9.9 ± 2.2	NS
Fetal pH (z scores)	−0.8 ± 1.2	−0.3 ± 1.5	NS
Fetal Po_2 (z scores)	−0.5 ± 0.8	−0.7 ± 0.6	NS
β Endorphin* (pg/ml)	77.0 (47–448)	55.5 (36–114)	NS
Cortisol (ng/ml)	21.4 ± 8.5	15.8 ± 5.6	NS
MCA PI	1.89 ± 0.32	1.85 ± 0.25	NS
Fetal heart rate (beats/min)	134.8 ± 8.0	139.7 ± 10.7	NS
Time to access* (min)	3.5 (1.0–9.2)	3.1 (1.1–6.5)	NS
Duration* (min)	14.3 (6.4–42.9)	10.5 (5.0–33.1)	NS
Volume (% FPV)	16.3 ± 7.5	16.4 ± 7.4	NS

Mean ± SD unless otherwise stated.

* Median and range.

IHV = intrahepatic vein; NS = not significant; Po_2 = partial pressure of oxygen; MCA PI = middle cerebral artery pulsatility index; FPV = fetoplacental blood volume.

Table 2. Baseline data for Cross-sectional Comparison of Different Fetuses Undergoing Either PCI Transfusions, IHV Transfusions without Fentanyl, or IHV Transfusions with 10 μg/kg Fentanyl

	PCI Transfusion (n = 15)	IHV Transfusion (n = 14)	IHV with Fentanyl (n = 16)	Significance (ANOVA)
Gestational age (weeks)	30.4 ± 3.4	27.2 ± 4.2	29.6 ± 3.1	NS
Fetal hemoglobin (g/dl)	9.2 ± 2.5	10.1 ± 2.1	9.6 ± 2.1	NS
Fetal pH (z scores)	−0.3 ± 1.0	−0.8 ± 0.9	−0.2 ± 1.6	NS
Fetal Po_2 (z scores)	−0.5 ± 0.8	−0.4 ± 0.8	−0.9 ± 0.8	NS
β Endorphin* (pg/ml)	53 (26–133)	66 (31–162)	55.5 (34–114)	NS
Cortisol* (ng/ml)	17 (9–49)	18 (9–28)	13 (11–31)	NS
MCA PI	1.91 ± 0.38	2.01 ± 0.34	1.92 ± 0.33	NS
Fetal heart rate (beats/min)	142.0 ± 9.5	143.5 ± 9.5	138.5 ± 10.5	NS
Time to access* (min)	0.8 (0.1–3.8)	3.3 (0.4–9.3)	2.3 (0.4–6.5)	$P = 0.004$
Duration* (min)	10.0 (2.4–23.7)	16.3 (4.1–39.6)	10.8 (5.0–33.1)	NS
Volume* (% FPV)	6.8 (2.0–14.9)	3.7 (1.8–11.5)	7.4 (2.0–14.4)	NS

Mean ± SD unless otherwise stated.

* Median and range.

PCI = placental cord insertion; IHV = intrahepatic vein; ANOVA = analysis of variance; NS = not significant; Po_2 = partial pressure of oxygen; MCA PI = middle cerebral artery pulsatility index; FPV = fetoplacental blood volume.

five waveforms. As in previous studies,[11,12] we did not correct PI for individual fetuses' changes in heart rate, as neither we nor other investigators have observed any correlation between MCA PI and fetal heart rates within the normal range.[24] The intraobserver coefficient of variation for PI was 2%.

Study Design

Given the ethical and clinical constraints of research during risky intrauterine procedures, randomization of sampling site was considered inappropriate as anatomic factors usually favor one approach over the other. In addition, placebo administration in controls was not considered compatible with the principle for nontherapeutic research in children of avoiding anything other than trivial risk procedures; this would have necessitated an additional bolus injection of saline with an attendant risk of cord tamponade.

Thus, the effect of 10 μg/kg fentanyl on the fetal response to IHV transfusion was assessed in a longitudinal analysis of 12 fetuses that underwent one IHV transfusion with fentanyl and one IHV transfusion without fentanyl, and a cross-sectional analysis of all 16 fetuses that underwent IHV transfusion with fentanyl compared with an additional 29 fetuses transfused without fentanyl at either the PCI or IHV (fig. 1). It was not possible in the longitudinal group to standardize fentanyl procedures for IHV transfusion order. Some patients were reluctant to have fentanyl at the first or second transfusion, particularly if they had not undergone transfusion in previous pregnancies, but then consented to fentanyl at a subsequent transfusion.

Statistical Analysis

Continuous variables were compared at baseline using paired or unpaired Student *t* test, unless they were not consistent with normal distribution, in which case the Wilcoxon signed rank or Mann–Whitney tests were used. To control for gestation, blood gas values were expressed as gestation-independent z scores,[25] and volume transfused was expressed as a percentage of estimated fetoplacental blood volume.[26] Changes with transfusion were expressed as delta values (Δ = post-transfusion − pretransfusion).

In the longitudinal comparison, Δ values were compared using the one-sample *t* test, whereas in the cross-sectional comparison, significance was sought using factorial analysis of variance for normally distributed data, or otherwise the Kruskal Wallis test. The least squares method was used for regression analyses on log-transformed data where appropriate. All analyses were two-tailed, and $P < 0.05$ was considered significant. Data for some of the control fetuses have been reported elsewhere.[12,13]

Results

In the initial pilot experiments, 3 μg/kg fentanyl failed to ablate fetal stress responses. IHV transfusion between 27 and 32 weeks produced a cortisol response in all seven fetuses, whereas four of seven Δ β endorphins and two of five Δ MCA PI values remained in the range reported previously after procedures without analgesia. Thus, we proceeded to use 10 μg/kg fentanyl, which was given to 16 fetuses before IHV transfusion. Fentanyl was not detected in pretransfusion fetal blood samples but was in all samples after transfusion with 10 μg/kg fentanyl (median, 0.91 ng/ml; range, 0.16–4.26 ng/ml). Fentanyl concentrations declined with time as shown in figure 2 ($\log y = 0.83 - 0.87 \log x$; $r = -0.53$; $P = 0.03$). There were no immediate complications during or after fentanyl transfusions, which were not associated with any change in umbilical artery Doppler waveform.

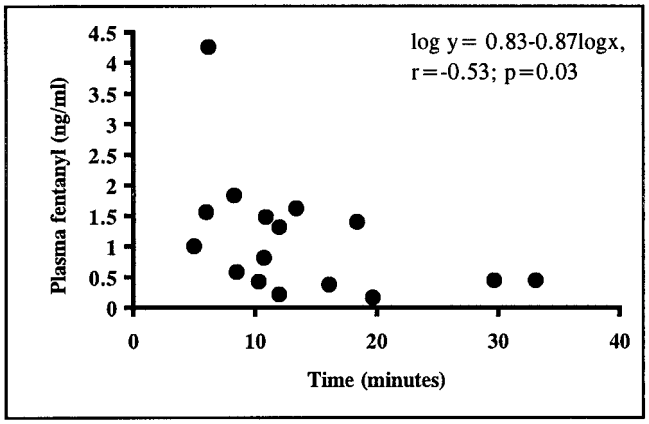

Fig. 2. Posttransfusion fentanyl concentrations in fetal venous plasma as a function of time from 10 μg/kg fentanyl administration.

Longitudinal Analysis

Twelve fetuses in the study group had comparable data collected at an IHV transfusion without fentanyl either before (n = 5; median, 2 weeks) or after the fentanyl transfusion (n = 7; median, 3 weeks). Baseline and transfusional parameters were similar for fentanyl and nonfentanyl transfusions (table 1). Complete Doppler data were available for five subjects. As expected, control IHV transfusions were associated with significant increases in β endorphin (mean Δ, 135 pg/ml; 95% confidence interval [CI], 81.1–189) and cortisol (mean Δ, 23 ng/ml; 95% CI, 11.5–34.5), and a significant decrease in MCA PI (mean Δ, −0.63; 95% CI, −0.97 to −0.29; fig. 3).

The β-endorphin response to transfusion in the presence of fentanyl was significantly lower than with nonfentanyl transfusions (mean difference in Δ values, −70.3; 95% CI, −121 to −19.2; one-sample $t = -2.7$; $P = 0.02$), although the response was still significant (mean Δ, 64.8 pg/ml; 95% CI, 41.2–88.3). The cortisol response (mean Δ, 12.1 ng/ml; 95% CI, 4.5–19.6) was lower with fentanyl transfusions, but the difference was not significant (mean difference in Δ values, −10.9; 95% CI, −24.7 to 2.9; $t = -1.7$; $P = 0.11$). Fentanyl abolished the MCA PI response (mean Δ, 0.01; 95% CI, −0.09 to 0.12), which was thus significantly different from IHV transfusions without fentanyl (mean difference in Δ values, 0.65; 95% CI, 0.26–1.04; $t = 3.2$; $P = 0.03$). This was not a result of any alteration in instantaneous fetal heart rate, which did not change significantly in either group.

Cross-sectional Analysis

The three groups were comparable for baseline and transfusional variables (table 2) with the exception of time to access, which, as previously shown, is shorter for PCI transfusions.[10] Complete Doppler data were available for 7 of the 16 fentanyl transfusions, 11 of the 15 PCI transfusions, and 11 of the 14 control IHV transfusions. There was no significant response in any stress variable to transfusion at the PCI (mean Δ β endorphin, 12.8 pg/ml; 95% CI, −8.0 to 33.6; mean Δ cortisol, 1.1 ng/ml; 95% CI, −5.1 to 7.2; mean Δ MCA PI, −0.11; 95% CI, −0.43 to 0.22).

As shown in figure 4, the response to transfusion differed significantly between the three groups (Δ β endorphin, $F = 9.6$, $P < 0.001$; Δ cortisol, $F = 6.0$, $P < 0.01$; Δ MCA PI, Kruskall Wallis $H = 6.6$, $P = 0.04$). Both the β-endorphin and the MCA PI responses after fentanyl were similar to PCI transfusions and significantly less than after IHV transfusion without fentanyl ($P < 0.01$ and $P = 0.02$, respectively). In contrast, the cortisol response after fentanyl remained significantly greater than after PCI transfusions ($P = 0.04$), but not statistically different from that after IHV transfusions without fentanyl ($P = 0.16$). Again, there was no significant change in instantaneous fetal heart rate in any of the three groups.

Discussion

This study shows that direct administration of 10 μg/kg fentanyl blunts the fetal stress response to intrauterine needling. The magnitude of the β-endorphin and cortisol response was halved, and the cerebral Doppler response was ablated. Results were consistent in the two comparisons: paired IHV transfusions in the same fetuses and unpaired IHV and PCI transfusions in different fetuses.

Fentanyl significantly attenuated the endorphin and cerebrovascular response, but not the cortisol response. This differential effect is not surprising. Using the same dose, Anand *et al.*[3] found that intravenous fentanyl in preterm babies ablated most of the stress responses to surgery, but the reduction in the cortisol response after fentanyl failed to achieve statistical significance. Even high-dose fentanyl is known not to block established cortisol responses to surgery.[27] However, anesthetic doses of sufentanil have been shown to block the cortisol response to surgery in newborns.[4]

It is possible that the analgesic dose we used may have been too low. We based our dose of 10 μg/kg on the study by Anand *et al.*[3] in preterm neonates undergoing anesthesia for ductal ligation. Because little is known of direct fetal pharmacokinetics, we adjusted this dose for the additional placental circulation as per standard clinical practice.[28] The pharmacokinetic curve in figure 2 shows that fentanyl was detected in the fetal circulation. Concentrations (median, 0.9 ng/ml) were higher than the fetal concentrations achieved after a maternal 2-μg/kg bolus dose (median, < 0.5 ng/ml)[29] but less than those reported after higher-dose fentanyl in newborns (> 7 ng/ml).[30,31]

It is unlikely that the Doppler response to IHV transfusion without fentanyl represents a primary hemody-

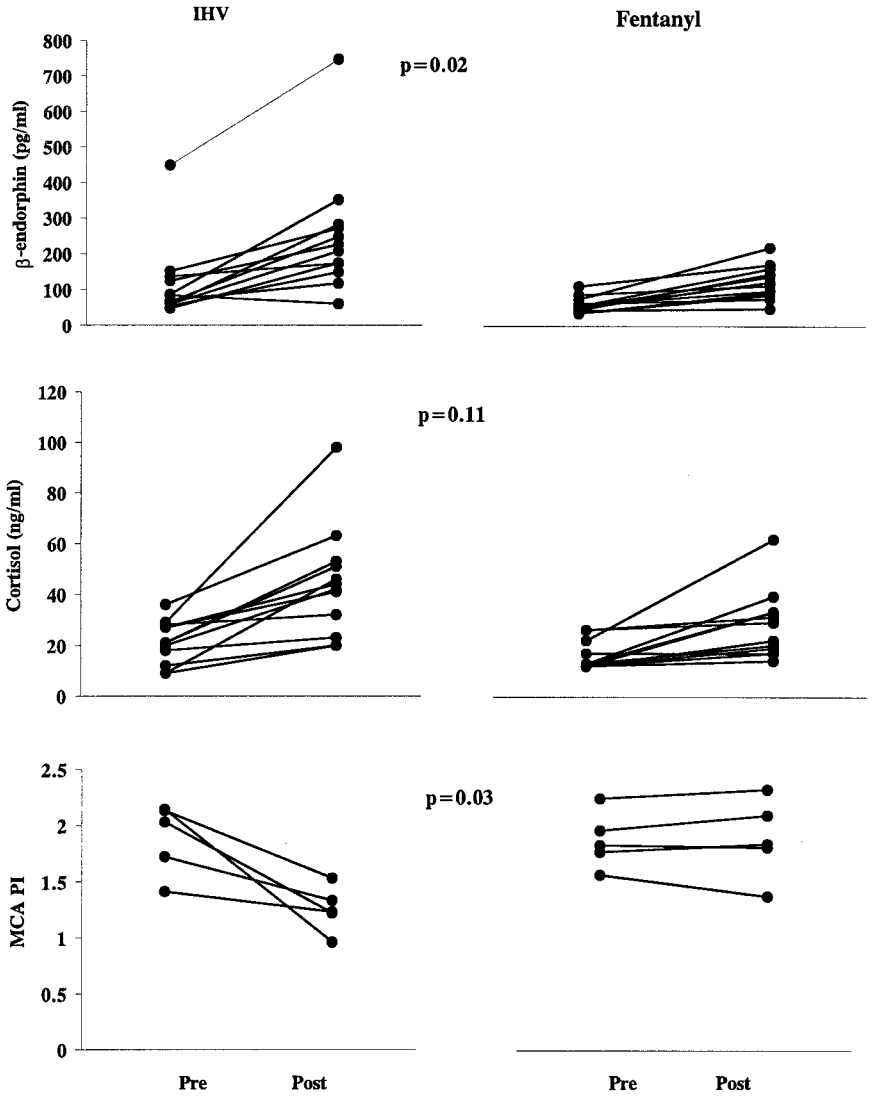

Fig. 3. Fetal β endorphin, cortisol concentrations, and middle cerebral artery pulsatility index (MCA PI) before and after intrahepatic vein (IHV) procedures in 12 fetuses transfused once with and once without fentanyl. *P* values are for the difference in responses between procedures with and without fentanyl, by one-sample *t* tests.

namic response as no response is seen after transfusion at the PCI,[11,12] IHV sampling without transfusion is associated with both a noradrenaline response[9] and an MCA PI response,[12] and non–blood sampling procedures that puncture the fetal trunk produce a similar MCA PI response to IHV procedures.[12]

Fentanyl completely blocked the MCA Doppler response. Although the mechanism of the fetal brain-sparing response is poorly understood, blockade experiments suggest that endogenous opioids reduce fetal peripheral vasoconstriction in response to asphyxial stress.[32] Fentanyl in doses of 10 μg/kg or greater has been shown to block circulatory responses to neonatal surgery.[33] Thus, fentanyl-induced vasodilation remains a possible explanation, at least for the Doppler changes.

Control data confirmed the validity of our end points, with absent responses to PCI transfusion and with responses to IHV transfusion comparable to those established previously.[10,12,13] Control transfusions had comparable baseline parameters to the fentanyl transfusions, with the exception of a shorter time to access in PCI transfusions. PCI sampling, being technically easier, is known to be quicker than IHV sampling.[10] However, time to access has not been shown to influence the degree of response, in contrast to the duration of transfusion that correlates linearly with all three responses.[9,12] The magnitude of the cortisol but not the β-endorphin or Doppler response, is also known to be influenced by gestation.[12,13] However, there was no significant difference in transfusion duration or gestation between the three types of transfusion.

Studies like ours are necessarily pragmatic, operating within the considerable ethical and practical constraints of interventive fetal research during risky, clinically indicated invasive procedures in ongoing pregnancies. As in studies of transplacental opioids during intrauterine procedures,[34] this study was designed so as not to interfere with, and thus not increase the risks of, the clinical procedure. Accordingly, randomization in such studies has been deemed inappropriate.[34] For similar reasons, analgesia was administered in this study on accessing the circulation, *i.e.*, after the stressful insult had com-

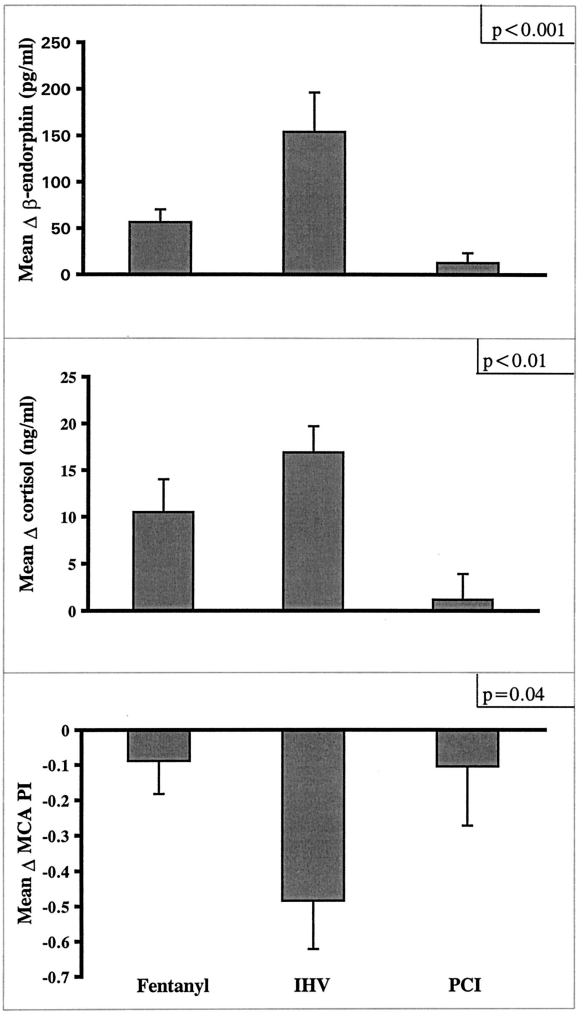

Fig. 4. The β-endorphin, cortisol, and middle cerebral artery pulsatility index (MCA PI) responses were each significantly different between fetuses transfused at the placental cord insertion (PCI), at the intrahepatic vein (IHV) without fentanyl, and at the IHV with fentanyl, by analysis of variance. Mean values and 95% confidence intervals are shown.

menced. Although our conclusions are strengthened by the two-model design with comparable findings in the longitudinal and cross-sectional analyses, we acknowledge that lack of randomization means that temporal effects or subject–operator–institutional factors cannot be discounted.

Giving analgesia to the fetus before the insult commences poses a considerable challenge.[5] A variety of fetal routes could be used: intraamniotic, intramuscular, or intravenous *via* the PCI. Each involves an additional invasive procedure, and thus a small risk of procedure-related fetal loss or delivery. Intraamniotic injection of lipid-soluble opioids results in subtherapeutic fetal concentrations.[35] Transplacental administration *via* the mother may be appropriate for open fetal surgery or termination, although general anesthesia is increasingly avoided in modern obstetric practice, and most fetal medicine procedures are performed on an outpatient basis. Benzodiazepines cross the placenta readily[36] but may cause maternal sedation, while their long half-life in the fetus may cause adverse behavioral effects if delivery soon follows. Opioids such as fentanyl cross the placenta less readily with fetomaternal ratios of approximately one third,[37] and when used in an outpatient setting, they do not reduce fetal movements,[34] so that continuous infusion would be required in the mother. Although opiate administration improves outcome in neonatal surgery,[4] enthusiasm for use of analgesia in the fetus must be tempered against the possibility of adverse effects at a time when the fetal nervous system is undergoing dramatic changes in neuroreceptor number and function.[8]

Although the human fetus in the last half of gestation has the necessary neuroconnections for nociception, it is not known whether the human fetus experiences pain. Nociception is difficult enough to study in the human neonate, but the intrauterine environment precludes study before birth of the behavioral manifestations of pain that can be observed postnatally. To explore the question of fetal nociception, our group has used fetal stress responses as an indication of the trauma involved to test the null hypothesis that pain responses would seem unlikely in the absence of stress responses. This study confirms that invasive procedures produce stress responses and shows that these can be blocked by analgesia. Because the relation between stress responses and pain is not clear, it is not possible from our data to conclude that the human fetus experiences pain *in utero*.

This study provides the first evidence that direct fetal analgesia reduces stress responses to intervention *in utero*. Further experiments are now indicated using higher-dose fentanyl, as well as studies using different drugs and different modes of administration.

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